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ORIGINAL RESEARCH

Routine screening and rates of metabolic syndrome in patients treated with clozapine and long-acting injectable antipsychotic medications: a cross-sectional study

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Objectives. To examine the rate of monitoring of metabolic syndrome and actual rates of metabolic syndrome in two patient cohorts [clozapine treatment and long-acting injectable (LAI) antipsychotic] who are reviewed on an equally regular basis (1–4 weekly) for administration of treatment.

Methods. Clinical and laboratory data are examined on 119 patients treated with clozapine and 116 patients treated with LAI antipsychotic medications to determine the rates of metabolic syndrome and evidence of monitoring for metabolic syndrome in the previous 6 months. Individuals with insufficient data from these cohorts were invited to attend for metabolic screening to determine actual rates of metabolic syndrome in these two cohorts of patients.

Results. All metabolic parameters were monitored to a significantly greater extent in the clozapine cohort (>90%), compared to those treated with LAI antipsychotic medications (<50%) (blood pressure, weight, lipid and glucose levels; $p < 0.001$). Metabolic syndrome was present in 38.9% of those treated with clozapine compared to 31.1% of patients treated with LAI antipsychotic medications ($X^2 = 0.54$, $p = 0.46$).

Conclusions. These findings suggest that a robust screening plan should be in place to monitor for metabolic syndrome in individuals treated with LAI antipsychotic medications. This screening should include measurement of body weight, waist circumference, fasting glucose, lipids and fasting insulin levels. Early recognition of abnormal metabolic parameters allows early intervention, therefore, improving long-term cardiovascular outcomes.

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Key words: Clozapine, LAI antipsychotics, metabolic syndrome, routine monitoring.

Introduction

Significant treatment advances have taken place in recent years for the management of schizophrenia. Despite such advances in treatment, individuals with schizophrenia on average have a 13–15-year shorter life expectancy than healthy controls, with the causes of this shorter life expectancy predominantly related to the co-morbid presence of chronic physical conditions, particularly coronary heart disease and type 2 diabetes (Hennekens *et al*. 2005; Saha *et al*. 2007; Laursen *et al*. 2014; Hjorthoj *et al*. 2017). This association between reduced life expectancy and physical morbidity has been attributed in part to engagement in an unhealthy lifestyle and a possible genetic predisposition (Hakko *et al*. 2011). Unhealthy lifestyle factors relate significantly to negative and cognitive symptoms of schizophrenia, with a less healthy diet, reduced engagement in exercise and increased cigarette smoking in comparison with healthy peers reported (De Leon & Diaz, 2005). Antipsychotic medication is central to the treatment of schizophrenia. However, it is now well recognised that antipsychotic medication and particularly second-generation antipsychotic medications (SGAs) are associated with significant cardiovascular side effects and an increased rate of type 2 diabetes (De Hert *et al*. 2011). In addition to a pre-existing metabolic risk for individuals with schizophrenia, antipsychotic medications have now consistently been associated with causing metabolic dysregulation (Ahmed *et al*. 2008; Hasnain *et al*. 2010).

Metabolic syndrome is a collective term used to describe a cluster of medical parameters including central and abdominal obesity, dyslipidaemias,

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Table 1. *International Diabetes Federation (IDF) criteria for metabolic syndrome*

	Males	Females	OR
Waist circumference	≥94 cm	≥80 cm	–
Blood pressure	Systolic BP ≥ 130 mm Hg or diastolic BP ≥ 85 mm Hg		Treatment of previously diagnosed hypertension
HDL cholesterol	<40 mg/dl (1.03 mmol/l)	<50 mg/dl (1.29 mmol/l)	Specific treatment for this lipid abnormality
Triglyceride	≥150 mg/dl (1.7 mmol/l)		Specific treatment for this lipid abnormality
Glucose	Fasting plasma glucose ≥ 100 mg/dl (5.6 mmol/l)		Previously diagnosed type II diabetes

HDL, high-density lipoprotein.

glucose intolerance, hyperinsulinemia and hypertension (Thakore, 2005). Any patient suffering from disorders associated with metabolic syndrome has an increased likelihood of developing heart disease, type 2 diabetes and experiencing cerebrovascular accidents (Alberti *et al*. 2005). The International Diabetes Federation (IDF) has developed diagnostic criteria for the screening and diagnosis of metabolic syndrome. The diagnostic parameters used by the IDF are presented in Table 1 (Alberti *et al*. 2006).

An individual is diagnosed with metabolic syndrome if they meet three of the five criteria listed in Table 1. This diagnostic tool accounts for prior and present disorders associated with each of the criteria. For example, if a patient is undergoing treatment for pre-diagnosed hypertension, they automatically meet the abnormal blood pressure criterion associated with metabolic syndrome (Alberti *et al*. 2005).

The World Health Organisation has cautioned that rates of metabolic syndrome are increasing (Lorenzo *et al*. 2007), but a large discrepancy remains between the rates of metabolic syndrome in the general adult population compared to a population of patients with a psychiatric diagnosis. For example, Bly *et al*. (2014) identified rates of metabolic syndrome in cohorts of individuals with bipolar disorder and schizophrenia of 33% and 47% compared to rates of 17% and 11% in healthy controls matched for age and gender from the National Health and Nutrition Examination Survey (NHANES).

Some SGAs, including clozapine, have been particularly associated with metabolic dysregulation and high rates of metabolic syndrome (De Hert *et al*. 2006). Clozapine is the treatment of choice for the management of treatment-resistant schizophrenia, a cohort comprising approximately 25% of patients with schizophrenia (Lamberti *et al*. 2006). The estimated prevalence of metabolic syndrome in individuals treated with clozapine has been demonstrated to be between 28% and 45% (Gianfrancesco *et al*. 2002), with the potential for metabolic side effects to develop shortly after treatment initiation. This can include significant weight gain, lipid abnormalities and heightened risk of developing type 2 diabetes (Henderson *et al*. 2000). Other SGAs and first-generation antipsychotic medications (FGAs) have also been associated with increased rates of metabolic dysregulation and metabolic syndrome although there are comparatively less studies exploring this association for FGAs (Hirsch *et al*. 2017).

Given this high propensity for metabolic dysregulation, even early in treatment with clozapine, it is optimal to regularly review individuals for metabolic dysregulation. Guidelines such as the Maudsley Guidelines (Taylor *et al*. 2018) provide information on the recommended frequency of monitoring of the parameters of metabolic syndrome. Clozapine guidelines dictate at least weekly full blood count (FBC) monitoring until 18 weeks of treatment with subsequent fortnightly monitoring until 52 weeks of treatment and monthly monitoring thereafter. Such regular monitoring for neutropenia and agranulocytosis makes it possible to incorporate regular metabolic monitoring, albeit such monitoring unlike FBC testing is not mandatory. In comparison, individuals treated with LAI antipsychotic medications do not require the same level of monitoring, but are frequently reviewed by mental health staff for the administration of treatment (every 1–12 weeks). Despite the risk of metabolic dysregulation and metabolic syndrome with antipsychotic medications, screening for metabolic syndrome (or aspects of metabolic syndrome) by either psychiatrists or primary care physicians is often sub-optimal (Barnes *et al*. 2007; Brunero & Lamont, 2009; Waterreus & Laugharne, 2009). Furthermore, it remains unclear, if responsibility for metabolic monitoring and

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management of abnormalities lies with primary or secondary care. Such ambiguity is unhelpful for a patient group with severe mental illness (Citrome & Yeomans, 2005).

Current guidelines or suggestions for the frequency of monitoring metabolic parameters in patients treated with antipsychotic medications are varied. For example, the American Diabetes Association suggests monitoring patients every 3 months (American Diabetes Association, 2004), whilst other researchers suggest monitoring at baseline, 6 months and then annually thereafter (Murtagh *et al*. 2011; Cohn, 2013).

This study was an observational prospective study conducted at Galway University Hospital with the aim of assessing the rate of monitoring of metabolic syndrome and actual rates of metabolic syndrome in two patient cohorts (clozapine treatment and LAI antipsychotic) who are reviewed on a very regular basis (1–4 weekly) for administration of treatment. We hypoth esised that patients prescribed LAI antipsychotic medications would be monitored less frequently than patients treated with clozapine and that the rates of metabolic syndrome would be higher in the clozapine cohort.

Methods

Subjects

Patients attending the adult West Galway Mental Health Services at Galway University Hospital for clozapine treatment ($n = 119$) or LAI antipsychotic treatment ($n = 117$) were invited to participate in the study. Individuals prescribed clozapine attended a dedicated clozapine clinic staffed by clinical nurse specialists. LAI antipsychotic medications were administered either at a day centre, an outpatient clinic or in their own residence by experienced community mental health nurses. Ethical approval was attained from the Galway University Hospitals Research Ethics Committee. Inclusion criteria for the study required patients to be treated with clozapine or a LAI antipsychotic medication for at least 6 months duration and be over 18 years of age. Individuals who attained clozapine on an outreach basis only ($n = 5$) or individuals with severe and enduring mental illness residing in one high-support residence who were treated with LAIs ($n = 6$) were not invited into the study due to concerns regarding their capacity to consent to participate in this study.

Procedures

Case notes

For individuals providing consent, clinical case notes and laboratory data were reviewed (January–April, 2018) to attain basic demographic and clinical data. Demographic data included age, gender, marital and employment or vocational status. Clinical data included psychiatric diagnosis, medications including dose of medications prescribed, alcohol, tobacco and psychoactive substance use. Medication data recorded included FGA, SGA other psychotropic agents and medications pertaining to physical health conditions associated with metabolic syndrome. All documented clinical or laboratory data pertaining to metabolic syndrome [such as body mass index (BMI), abdominal waist circumference, blood pressure, lipid profile data including cholesterol, triglyceride, high-lipid density (HDL), low-lipid density (LDL) and glucose or HbA1C] recorded at any stage over the previous 6 months prior to case note review were recorded. A diagnosis of metabolic syndrome was based on the IDF criteria (see Table 1; Alberti *et al.* 2006). The diagnostic parameters of weight circumference and fasting blood glucose were used in the first instance in accordance with IDF criteria. However, in circumstances where waist circumference or fasting blood glucose were unavailable, proxy measures of central obesity (BMI) or impaired glucose tolerance ($\text{HbA1C} \geq 42$ mmol/mol) were used, respectively.

Where clinical (BMI and/or waist circumference, blood pressure) or blood lipid data (cholesterol, triglycerides, LDL, HDL and glucose and/or HbA1C) had not been documented, participants (LAI = 71; clozapine = 6) were re-contacted and invited to attend an appointment for additional testing for metabolic syndrome.

All laboratory data examined were analysed at the biochemistry laboratory at University Hospital Galway.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) 24.0 for Windows (SPSS Inc., IBM, New York, USA). Descriptive analyses (frequencies, percentages, means and standard deviation) on key demographic and clinical data were performed for both categorical and continuous variables, as appropriate. The presence of monitoring for metabolic syndrome (and components of metabolic syndrome) and rate of monitoring of metabolic syndrome within the two study groups were calculated. We utilised the student *t*-test for parametric data and the Chi-Square ($\chi 2$) test for non-parametric data as appropriate. All statistical tests were two-sided, and the α level for statistical significance was 0.05.

Results

All clozapine participants agreed for their clinical notes to be accessed, and only one LAI participant declined access to their clinical notes. Demographic and clinical details pertaining to both groups (clozapine = 119,

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Table 2. *Demographic and clinical data*

Variable	Clozapine ($n = 119$) n (%)/mean (S.D.)	LAI antipsychotic ($n = 116$) n (%)/mean (S.D.)	X^2, p
Gender			
Male	85 (71)	75 (64.7)	0.95, 0.33
Female	34 (29)	41 (35.3)	
Age	42.8 (11)	51.4 (13.4)	0.55, <0.01
Relationship status**			
Single	100 (84)	92 (79)	1.03, 0.61
Partner/married	15 (13)	14 (12)	
Separated/divorced	3 (3)	7 (6)	
Employment status			
Unemployed	75 (63)	59 (51)	5.389, 0.148*
Employed	32 (27)	39 (34)	
In third-level education	10 (8)	11 (10)	
Retired	2 (2)	7 (6)	
Primary diagnosis			
Schizophrenia	119 (100)	100 (86)	25.8, <0.001*
Bipolar disorder	0 (0)	14 (12)	
Neurotic disorders	0 (0)	2 (2)	
Antipsychotic medications			
FGA	–	57 (49)	–
SGA	119 (100)	58 (50)	
Secondary diagnosis			
Hypertension	9 (8)	10 (9)	0.088, 0.814*
Type 2 diabetes	6 (6)	10 (9)	1.186, 0.310*
Hypercholesterolaemia	3 (3)	6 (5.)	1.121, 0.329*

FGA, first-generation antipsychotic; SGA, second-generation antipsychotic.
*Fishers exact test utilised for p value.
** Data not available on all participants.

LAI antipsychotic = 116) are presented in Table 2. Patients in the clozapine cohort had a younger mean age [42.8 (S.D. = 10.7) years *v.* (51.4 (S.D. = 13.4) years; $p < 0.01$] and were more likely to have a diagnosis of schizophrenia (100.0% *v.* 86.2%; $X^2 = 25.8$, $p < 0.01$) compared to the LAI antipsychotic cohort. No participants were treated with both clozapine and an LAI.

Monitoring for metabolic syndrome

Metabolic parameter monitoring data for both clozapine and LAI antipsychotic cohorts are presented in Table 3. Of note, all metabolic parameters were monitored to a significantly greater extent in the clozapine cohort (blood pressure, weight, lipid and glucose levels; $p < 0.001$). All clozapine participants had monitoring for hypertension compared to 39% of LAI participants ($X^2 = 104.4$, $p < 0.001$). Ninety-six percent of clozapine participants had their weight monitored compared to 24% of LAI participants ($X^2 = 126.1$, $p < 0.001$); however, abdominal circumference measurements were measured to a greater extent in the LAI antipsychotic cohort (15%) compared to the clozapine cohort (2%) ($X^2 = 13.3$, $p < 0.001$). Blood lipid monitoring was undertaken in 90–95% of clozapine participants compared to 41–45% of LAI participants, depending on the lipid measure ($p < 0.001$), with glucose monitoring similarly more prevalent in the clozapine cohort (95%) compared to the LAI cohort (41%) ($X^2 = 80.1$, $p < 0.001$).

Metabolic syndrome

The prevalence of metabolic syndrome was determined, based on patients who had sufficient data available to calculate this. Of those participants re-contacted due to a lack of clinical or blood lipid data, 24 (33.8%) individuals treated with LAI antipsychotic medications (who lacked haematological data) agreed to engage in further metabolic investigations, with none of the six invited participants treated with clozapine, agreeing to re-attend for additional investigations. All participants who declined the invitation to re-attend for additional monitoring agreed that existing clinical note data pertaining to rates of monitoring of metabolic syndrome could still be utilised.

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Table 3. *Monitoring for metabolic syndrome across clozapine and LAI treatment groups*

Monitoring of clinical variables	Clozapine ($n = 119$) n (%)	LAI antipsychotic ($n = 116$) n (%)	X^2, p
Blood pressure	119 (100)	45 (39)	104.37, <0.001
Weight measure			
Waist circumference	2 (2)	17 (15)	13.31, <0.001
Weight	114 (96)	27 (23)	128.70, <0.001
Any weight measure	114 (96)	28 (24)	126.14, <0.001
Lipids			
Cholesterol	113 (95)	52 (45)	68.21, <0.001
Triglycerides	113 (95)	52 (45)	68.21, <0.001
HDL cholesterol	113 (95)	52 (45)	68.21, <0.001
LDL cholesterol	107 (90)	48 (41)	59.49, <0.001
Glucose			
Blood glucose	42 (35)	24 (21)	5.50, 0.019
HbA1c	112 (94)	37 (32)	95.35, <0.001
Any glucose measure	113 (95)	47 (41)	80.12, <0.001

HDL, high-density lipoprotein; LAI, long-acting antipsychotic; LDL, low-density lipoprotein.

Table 4. *Rates of metabolic syndrome and parameters across both treatment groups*

	Clozapine n (%)	LAI antipsychotics n (%)	X^2, p
Metabolic syndrome*	44 (39)	14 (31)	0.54, 0.46
Metabolic syndrome parameters*			
Hypertension	26 (22)	19 (39)	4.24, 0.04
Obesity	57 (50)	19 (37)	1.81, 0.18
Dyslipidaemia	76 (67)	48 (67)	<0.01, 1.00
Glucose intolerance	31 (27)	22 (33)	0.44, 0.51
	Mean (S.D.)	**Mean (S.D.)**	t, p
BMI*	30.71 (5.31)	28.41 (6.31)	2.39, 0.02
Lipids*			
Cholesterol	4.93 (1.09)	5.13 (1.13)	0.25, 0.22
Triglycerides	2.21 (2.42)	2.22 (2.09)	0.02, 0.98
HDL cholesterol	1.22 (0.41)	1.30 (0.43)	1.34, 0.18
LDL cholesterol	2.79 (0.81)	2.89 (0.96)	0.75, 0.46
Glucose*			
Blood glucose	6.08 (2.51)	6.49 (4.13)	0.52, 0.60
HbA1c	37.27 (9.05)	38.62 (10.63)	0.83, 0.41

BMI, body mass index; HDL, high-density lipoprotein; LAI, long-acting antipsychotic; LDL, low-density lipoprotein.
*Data not available on all participants.

The rate of metabolic syndrome in the clozapine cohort compared to the LAI antipsychotic cohort was not statistically different (38.9% *v.* 31.1%, $X^2 = 0.54$, $p = 0.46$). The LAI antipsychotic-treated cohort had a higher rate of hypertension (38.8% *v.* 21.8%, $X^2 = 4.24$, $p = 0.04$). The clozapine cohort had a higher BMI ($t = 2.39$, $p = 0.018$) although there was no statistical difference in the rate of obesity between the two groups. There was no difference in the rates of dyslipidaemia, mean lipid, glucose or HbA1c levels between the two groups (see Table 4). Many patients in the LAI group had insufficient data

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available, and as such were not included in the above results.

In LAI participants, the treatment rate at study entry for those identified with abnormal parameters for hypertension ($n = 10$) was 52.6%, for type 2 diabetes ($n = 10$) was 45.5% and for hypercholesterolaemia ($n = 6$) was 12.5%. In clozapine participants, the treatment rate at study entry for those identified with abnormal parameters for hypertension ($n = 9$) was 34.6%, for type 2 diabetes ($n = 6$) was 19.4% and for hypercholesterolaemia ($n = 3$) was 3.9%.

Discussion

To our knowledge, this is the first study to specifically examine the prevalence of metabolic syndrome and the level of monitoring of metabolic variables across two specific groups of patients treated with either clozapine or LAI antipsychotic medication that are reviewed by mental health staff at approximately similar frequencies.

This study confirms our hypothesis that a significant discrepancy exists between the rates of monitoring for metabolic syndrome in patients treated with LAI antipsychotic medications compared to those treated with clozapine. This low rate of monitoring of patients treated with LAI antipsychotic medications for metabolic syndrome is consistent with some previous findings (Barnes *et al*. 2007; Mackin *et al*. 2007), with an audit of 21 mental health services, for example, in the UK, noting similarly low rates of monitoring of metabolic parameters (blood pressure (26%), BMI and/or other measures of obesity (17%), blood glucose or HbA1C (28%) and plasma lipids (22%) (Barnes *et al*. 2007). The potential benefits of improved screening measures for risk factors of metabolic syndrome in patients treated with LAI antipsychotic medications are also demonstrated in the literature. An audit of patients receiving depot antipsychotic medication (O'Callaghan *et al*. 2011) demonstrated a significant improvement in the monitoring of parameters for metabolic syndrome following the implementation of a screening checklist. In the re-audit process, the level of documentation was significantly improved, for example, weight recording increased from 1.6% to 61.1%. The more rigorous monitoring of the clozapine population potentially results from the significant emphasis on clinical monitoring for patients who are prescribed clozapine with blood tests on a regular basis – compulsory for those treated with clozapine compared to those treated with LAI antipsychotics. This monitoring structure provides an opportunity to regularly and consistently monitor the patient group for a variety of health conditions including metabolic parameters, in addition to the mandatory FBC monitoring. Unless specifically screened for, metabolic syndrome will be undetected (Isomaa *et al*. 2001). In some jurisdictions, patients attending mental health services have less access to general health care in comparison to a non-psychiatric patient group (Druss *et al*. 2001). While this is not generally the case in Ireland, it is possible that patients with enduring mental illness engage less with their primary care practice due to the nature of their illness with its associated negative and cognitive symptoms. Thus, a robust screening plan for metabolic syndrome is required, with close liaison between mental health services and primary care. For patient cohorts treated with LAIs and thus generally (but not always) in more frequent contact with mental health services, we would suggest that organisation of the location of such screening (primary care or with the mental health services) should be undertaken by mental health service staff in the first instance. Of note in this study, abnormal haematological or blood pressure findings detected after screening were communicated to their General Practitioner for the initiation of treatment for hypertension or type 2 diabetes as appropriate. On study commencement, six individuals in the clozapine cohort were treated with antihypertensive agents, three individuals were treated for type 2 diabetes and one individual was treated for hypercholesterolemia due to collaborative communication between clozapine staff and primary care after screening in the clozapine clinic. Similarly in the LAI cohort, six individuals were treated with antihypertensive agents, six individuals were treated for type 2 diabetes and one individual was treated for hypercholesterolemia due to metabolic screening in the mental health services with subsequent collaboration with primary care.

Our second hypothesis that patients treated with clozapine would have higher rates of metabolic syndrome was noted; however, this was not statistically significant. This reinforces the argument for a structured clinical monitoring process to be put in place for patients on LAI antipsychotic medications, to the same standard as for patients treated with clozapine. Following the initial period of data collection, patients who had no clinical or blood lipid data available for the previous 6-month period were invited to have these measurements taken. Despite this invitation, only an additional 24 patients treated with LAI antipsychotic medications actually availed of this metabolic screening (34%). It is possible that this patient group will require more than a single invitation such as this and will require regular prompts to engage in monitoring, with every effort made to remove the barriers to this process, for example, bringing a weighing scale, sphygmomanometer and equipment for phlebotomy on domiciliary visits.

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In relation to individual metabolic symptom parameters, approximately two-thirds of individuals in both cohorts demonstrated dyslipidaemia. Very low rates of pharmacological interventions (other non-pharmacological interventions may have been provided) at study entry were noted for individuals with abnormal lipid parameters. Dyslipidaemia has previously been reported to occur at particularly high rates with clozapine (Stroup *et al*. 2016; Ingimarsson *et al*. 2017); however, both FGA and SGA antipsychotic medications have been associated with lipid dysregulation (Buhagiar & Jabbar, 2019), as was demonstrated in this study. Hypertension was present at higher rates in the LAI antipsychotic group, albeit one recent study noted higher rates of hypertension in a cohort of clozapine patients (56%) than was noted in this study (Lappin *et al*. 2018). However, this study again highlights the need for individuals treated with LAI antipsychotic medications to have this simple to measure investigation regularly performed (similar to the clozapine-treated cohort). Both groups had a mean BMI in the obese range, with this significantly higher in the clozapine cohort. Whilst weight gain in enduring mental illness may occur for several different reasons, the link between obesity and antipsychotic medication is now well established with certain antipsychotic medications such as clozapine demonstrating, as in this study, a greater propensity for causing weight gain (Leucht *et al*. 2013).

This study was associated with a number of limitations. Firstly, proxy measures of central obesity (BMI) and impaired glucose tolerance (HbA1c) were utilised for some participants due to insufficient data pertaining to abdominal circumference and fasting blood glucose levels. Secondly, whilst we had a relatively large cohort of individuals treated with LAI antipsychotics, complete data to examine the presence of metabolic syndrome or individual parameters for metabolic syndrome were lacking, making it likely that our data represent an under-estimate of the rate of metabolic syndrome and rate of hypertension, dyslipidaemia and glucose intolerance. Insufficient clinical data were available to control for effect of potential confounders including different dietary regimes and severity of negative symptomatology. Additionally, insufficient power was present to examine the presence of metabolic syndrome across a range of different LAI antipsychotic medications. Precise data pertaining to treatment duration with antipsychotic medications were not attained in this study; however, no participant had recently been commenced on LAI or clozapine treatment. Future studies including a larger cohort of patients treated with a range of FGA and SGA LAI antipsychotics would be optimal. Finally, as this is a cross-sectional study, a longitudinal study of several years of duration would be optimal in identifying the rate of antipsychotic-related metabolic syndrome, which is planned as a future direction for this cohort of participants.

Conclusion

This study demonstrates the need for a robust screening plan for metabolic syndrome across all patients treated with antipsychotic medication and not just those on clozapine. This screening should include measurement of body weight, waist circumference, fasting glucose and lipids and fasting insulin levels. Early recognition of abnormal metabolic parameters allows early intervention, therefore, improving the long-term cardiovascular outcomes.

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Conflicts of interest

None.

Ethical standards

Ethical approval was obtained for the study from the HSE. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committee on human experimentation with the Helsinki Declaration of 1975, as revised in 2008.

Contributions

All authors participated in the design of the study, data attainment and critical review of the manuscript.

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